Male related

Male-Mediated Birth Defects and Disorders


Increased risk of death with congenital anomalies in the offspring of male semiconductor workers.

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Female workers in the semiconductor industry have higher risks of subfertility and spontaneous abortion, but no studies exploring male-mediated developmental toxicity have been published. This study aimed to investigate whether the offspring of male workers employed in the semiconductor manufacturing industry had an increased risk of death with congenital anomalies. The 6,834 male workers had been employed in the eight semiconductor companies in Taiwan between 1980 and 1994. We identified the live born children with or without congenital anomalies of the workers using the National Birth and Death Registries from the Department of Health, Taiwan. Multiple logistic regression models were used to estimate the odds ratios (OR) of birth outcomes and deaths, controlling for infant sex, maternal age, and paternal education. A total of 5,702 children were born to male workers during the period 1980-1994. There were increased risks of deaths with congenital anomalies (adjusted OR, 3.26; and 95% confidence interval [CI], 1.12-9.44) and heart anomalies (OR, 4.15; 95% CI, 1.08-15.95) in the offspring of male workers who were employed during the two months before conception. We found evidence of a possible link between paternal preconception exposure of semiconductor
manufacturing and an increased risk of congenital anomalies, especially of the heart. The possible etiological basis needs to be corroborated in further research.


Evidence for a role of paternal exposures in developmental toxicity.

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Experimental evidence from radiation exposure, antimitotic drugs or chemicals such as pesticides or metals does suggest the possibility of transmission of paternally mediated developmental effects across generations. The mechanistic framework is growing with suggestion of transmission of epigenetic modifications as a mechanism alternative to germ-line mutagenesis. There is also ample experimental evidence for a specific susceptibility of the male embryo to the action of endocrine disrupters. In parallel, interpretation of epidemiological findings regarding effects of well-characterized paternal exposures, such as ionizing radiation or persistent organic pollutants (dioxins), on intrauterine development remains equivocal. Many epidemiological studies have included paternal exposures as an add-on to existing studies and focused mainly on birth defects, sex ratio, childhood cancers or spontaneous abortions. Functional alterations such as neurobehavioural parameters or reproductive dysfunction resulting from paternal exposure have been barely studied. Improved knowledge on possible consequences of paternal exposures in future generations is needed and has strong implication in terms of regulation, in the workplace for instance. One may expect human studies to be
conducted with a particular focus on male-mediated developmental toxicity making use of biological markers pertinent to hypothesized mechanisms. Recognition of early determinants of disease onset has led to the setup of a number of mother-child cohorts across the world and careful assessment of paternal exposures should be included in these studies. These cohorts will also have the power to evaluate the specific impact of in utero exposure on a number of endpoints of developmental toxicity in males.

PMID: 18226072 [PubMed – indexed for MEDLINE]


Paternal exposures and the question of birth defects.

Poynor DH, Lupkiewicz S, Sage SR, Carver VH, Kousseff BG, Lubs HA, Williams CA.

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Compared to maternal exposures, little attention has been paid to the possibility of paternally induced adverse effects on fetal development. There is increasing concern, however, about the potential for male-mediated developmental toxicity brought about by exposure to teratogenic agents. This is evidenced by the number of calls regarding paternal exposures that are received by teratogen information services. In this paper, we report the experience of the state of Florida’s Teratogen Information Services regarding questions asked about paternal exposures, and briefly review what is known about the risk of paternal exposure to the 10 agents which are most frequently queried.

PMID: 9260438 [PubMed – indexed for MEDLINE]

Paternal exposures: impact on reproductive and developmental outcome. An overview.

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Experimental and epidemiologic investigations document the adverse consequences of an array of paternal exposures on the development of subsequent offspring. Male-mediated abnormalities have been reported after exposure to therapeutic and recreational drugs, to chemicals in the workplace and environment and to ionizing radiation. The impact on progeny outcome includes: an increase in congenital malformations, spontaneous abortions, fetal resorptions; low birth weight; increase in childhood cancers; developmental, neurobehavioral, neuroendocrine, neurochemical abnormalities; effects in F2 generation progeny. Fertility is often unaffected. The comparative influence of genetic, epigenetic and nongenetic mechanisms in the etiology of paternally-mediated adverse outcomes is unknown. There is no a priori reason to assume that male-mediated effects are limited to the agents studied to date. The broad spectrum of alterations recorded after exposure to a variety of unrelated agents suggests the need for a more focused effort and multidisciplinary exploration of the potential impact of the male parent on reproductive outcome.

PMID: 8981601 [PubMed – indexed for MEDLINE]


A case-control study of paternal smoking and birth defects.

Zhang J, Savitz DA, Schwingl PJ, Cai WW.
A stratified random sample of 29 hospitals in the Shanghai Municipality, China, was used to select 1012 birth defects cases and controls. Mothers of the cases and controls were interviewed in the hospitals from October 1986 to September 1987…

The relative risk (RR) of birth defects associated with paternal smoking was 1.2. Paternal smoking was associated with a 2.1-fold increase of anencephalus; infants whose fathers smoked were 3.3 times as likely to have had pigmentary anomalies of the skin, and 2.3 times as likely to have a diaphragmatic hernia. The odds ratio (OR) of spina bifida was 1.9 and varus or valgus deformities of feet had an OR of 1.8. The OR of these anomalies was also over 1.5: eye anomalies, microtia or absence of ear, nasal bone absence, cleft palate without cleft lip, brachydactyilia or adactyilia, undescended testicle, and polycystic kidney. The possible dose-response relationship between paternal smoking and birth defects was assessed in 3 groups: 1-9, 10-19, and 20 or more cigarettes per day. Similar increased RRs across smoking levels were found for anencephalus, cleft palate, and pigmentary anomalies of the skin. Increasing risk among the heavier smokers was apparent for spina bifida, nasal bone absence, varus or valgus deformities of the feet, and diaphragmatic hernia. Paternal smoking was slightly more related to multiple defects than to single defects. This suggests a modest link between paternal smoking and total birth defects and a stronger effect of paternal smoking and anencephalus and spina bifida risk, consistent with a previous study.

PMID: 1428480 [PubMed – indexed for MEDLINE]

Male-mediated developmental toxicity in mice after 8 weeks’ exposure to low doses of X-rays.

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PURPOSE: The aim of the study was to investigate the effects of subchronic irradiation of male mice on reproduction ability and induction of male-mediated teratogenesis. MATERIALS AND METHODS: Male mice were irradiated to 0.05 Gy, 0.10 Gy and 0.20 Gy daily for 8 weeks, 5 days per week. The total doses were 2.00 Gy, 4.00 Gy and 8.00 Gy, respectively. After the end of exposure each male was caged with two untreated females. The females were sacrificed on day 17 based on the finding of a vaginal plug. Females were examined for the number of live and dead implantations and the incidence of congenital malformations of survival foetuses. RESULTS: The fertilization ability of males was not diminished. The exposure to 0.20 Gy daily significantly decreased the percent of pregnant females and the number of total implantations. Exposure to 0.10 Gy and 0.20 Gy daily caused decreases in the number of live foetuses and induced dominant lethal mutations (over 50% at the highest dose). Exposure to each dose significantly enhanced the number of deaths (especially early) implants. The incidence of gross and skeletal malformations was not statistically significant, except for skeletal malformations at the highest dose. CONCLUSIONS: Results confirmed that irradiation of male germ cells cause genetic effects which could be transmitted to the offspring. After subchronic exposure to low doses the majority of mutations caused premature death. Subchronic exposure to low doses of X-rays did not induce external and skeletal malformations of surviving foetuses.
In recent years, the public has become more aware that exposure of males to certain agents can adversely affect their offspring and cause infertility and cancer. The hazards associated with exposure to ionising radiation have been recognised for nearly a century, but interest was aroused when a cluster of leukaemia cases was identified in young children living in Seascale, close to the nuclear processing plant at Sellafield in West Cumbria. There was a civil court case on behalf of two of the alleged victims of paternal irradiation at Seascale against British Nuclear Fuels. The case founderered on “the balance of probabilities”. Nevertheless, there was support for paternal exposure from Japanese experimental X-ray studies in mice. The tumours were clearly heritable as shown by F2 transmission. Also, effects of a relatively non-toxic dose of radiation (1Gy) on cell proliferation transmitted to the embryo were manifested in the germ line of adult male mice even after two generations. In addition in humans, smoking fathers appear to give rise to tumours in the F(1) generation. Using rodent models, developmental abnormalities/congenital malformations and tumours can be studied after exposure of males in an extended dominant lethal assay and congenital malformations can be determined which have similar manifestations in humans. The foetuses can also be investigated for skeletal malformations and litters can be allowed to
develop to adulthood when tumours, if present, can be observed. Karyotype analysis can be performed on foetuses and adult offspring to determine if induced genetic damage can be transmitted. Using this study design, cyclophosphamide, 1,3-butadiene and urethane have been examined and each compound produced positive responses: cyclophosphamide in all endpoints examined, 1,3-butadiene in some and urethane only produced liver tumours in F(1) male offspring. This suggests the endpoints are determined by independent genetic events. The results from heritable studies with 1,3-butadiene have been used in the parallelogram approach to determine a risk assessment for the germ cells in man.

PMID: 16039685 [PubMed – indexed for MEDLINE]


Review of experimental male-mediated behavioral and neurochemical disorders.

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Paternal exposures to exogenous agents have been reported to produce a variety of developmental defects in the offspring. In experimental animals, these effects include decreased litter size and weight, increased stillbirth and neonatal death, birth defects, tumors, and functional/behavioral abnormalities—some of these effects being transmitted to the second and third generations. This article reviews the exogenous agents that have reportedly caused behavioral or neurochemical alterations in offspring of experimental animals following paternal exposures, including advanced age, alcohols,
cyclophosphamide, ethylene dibromide, lead, opiates, and a few miscellaneous chemicals. Based upon the consistency of effects in several of these agents in a variety of studies in experimental animals, the conclusion is that paternal exposures may contribute to the incidence of neurobehavioral disorders in humans.

PMID: 8947937 [PubMed – indexed for MEDLINE]


Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry.

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OBJECTIVES: The purpose of the study was to determine whether paternal occupational exposure to dioxin-contaminated chlorophenols is associated with an increased risk of congenital anomalies or other adverse reproductive outcomes in offspring.

METHODS: As a result of a multistep linkage, 19675 births between 1952 and 1988 were identified as children of a cohort of 9512 fathers who had worked at least one year in British Columbia sawmills where chlorophenate wood preservatives had been used. A nested case-referent analysis was applied, using conditional logistic regression, with five referents matched per case according to year of birth and gender. Chlorophenate exposure was based on expert raters’ estimations of hours of exposure applied to specific time windows prior to birth. RESULTS: The offspring of male sawmill workers were at increased risk for developing congenital anomalies of the eye, particularly congenital cataracts; elevated risks for developing anencephaly or spina bifida and congenital anomalies of
genital organs were shown according to specific windows of exposure. No associations were found for low birthweight, prematurity, stillbirths, or neonatal deaths. CONCLUSIONS: The study adds further support to the hypothesis of male-mediated developmental toxicity. Paternal exposure to chlorophenates was associated with the development of certain congenital anomalies in offspring.

PMID: 8881015 [PubMed – indexed for MEDLINE]


Male-mediated teratogenesis: spectrum of congenital malformations in the offspring of A/J male mice treated with ethylnitrosourea.

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Male mice of inbred strain A/J were intraperitoneally treated with ethylnitrosourea (ENU). On day 64-82 posttreatment, the males were mated with untreated virgin females of the same strain. Copulation involved sperm that were spermatogonial stem cells at the time of treatment. On day 18 of gestation, viable fetuses were inspected for external malformations. The most common malformation to occur spontaneously in the control group was cleft palate or cleft lip. Similarly, in the ENU-treated series, cleft palate or cleft lip was the predominant malformation, the frequency (15%) of which was significantly increased in the highest dose group (5 x 50 mg/kg) compared to control (8%). Based on these results and other data, we propose that a large fraction of external
malformations in fetuses from mutagenized paternal germ cells are a result of increased yields of spontaneously occurring malformations.

PMID: 9178452 [PubMed – indexed for MEDLINE]


Exposure to PCBs and p,p’-DDE and human sperm chromatin integrity.


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Persistent organochlorine pollutants (POPs) such as polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (p,p’-DDE), the major metabolite of dichlorodiphenyltrichloroethane (DDT), are stable lipophilic compounds widely found in the environment and in the general population. They can enter the food chain, and their negative impact on male reproduction is currently under active scrutiny. To explore the hypothesis that environmental exposure to these compounds is associated with altered sperm chromatin structure integrity in human sperm, we conducted a study of 176 Swedish fishermen (with low and high consumption of fatty fish, a very important exposure source of POPs). We determined serum levels of 2,2′,4,4′,5,5′-hexachlorobiphenyl (CB-153) and p,p’-DDE, and we used the sperm chromatin structure assay (SCSA) to assess sperm DNA/chromatin integrity. When CB-153 serum levels (individual dose range, 39-1,460 ng/g lipid) were categorized into equally sized quintiles, we found an association with the DNA fragmentation index (%DFI). A significantly lower %DFI was found
in the lowest CB-153 quintile (< 113 ng/g lipid) compared with the other quintiles; there was a similar tendency, although not statistically significant, between %DFI and p,p’-DDE. These results suggest that POP exposure may have a slight negative impact on human sperm chromatin integrity.

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Relation between serum xenobiotic-induced receptor activities and sperm DNA damage and sperm apoptotic markers in European and Inuit populations

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Persistent organic pollutants (POPs) can interfere with hormone activities and are suspected as endocrine disrupters involved in
disorders, e.g. reproductive disorders. We investigated the possible relation between the actual integrated serum xenoestrogenic, xenoandrogenic and aryl hydrocarbon receptor (AhR) activities, and the sperm DNA damage and sperm apoptotic markers of 262 adult males (54 Inuits from Greenland, 69 from Warsaw (Poland), 81 from Sweden, and 58 from Kharkiv (Ukraine)) exposed to different levels of POPs. Xenobiotic-induced receptor activities were determined by receptor-mediated luciferase reporter gene expression. Sperm DNA damage was measured using terminal deoxynucleotidyl transferase-driven dUTP nick labeling assay (TUNEL) and pro- (Fas) and anti-apoptotic (Bcl-xL) markers were determined by immune methods. Different features of xenobiotic-induced receptor activity in serum and sperm DNA fragmentation and apoptotic markers existed between the Inuits and the European Caucasians. Negative correlations between xenobiotic-induced receptor activities and DNA damage were found for Inuits having relatively lower xenoestrogenic, lower dioxin-like activity, and lower sperm DNA damage, but higher xenoandrogenic activity. In contrast, in the European groups, xenobiotic-induced receptor activities were found to be positively correlated with the DNA damage. Further research must elucidate whether altered receptor activities in concerted action with genetic and/or nutrient factors may have protecting effect on sperm DNA damage of the Inuit population.


Paternal occupation and anencephaly.

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Abstract: It has been suggested that paternal occupational exposures to pesticides and solvents increase the risk of neural tube
defects in offspring. With the use of Texas livebirth, fetal death, and linked livebirth-death records, the authors conducted a population-based case-control study among 1981-1986 Texas births to examine the association between paternal occupation and anencephalic births. Fathers employed in occupations associated with solvent exposure were more likely to have offspring with anencephaly (odds ratio (OR) = 2.53), with painters having the highest risk (OR = 3.43). A lesser association was found for fathers employed in occupations involving pesticide exposure (OR = 1.28). Further studies are indicated to clarify these associations.


Paternal military service in Vietnam and the risk of late adverse pregnancy outcomes.

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Abstract: We conducted a case-control study of women who delivered infants from August 1977 until March 1980 at Boston Hospital for Women. Paternal military service history among 857 congenital anomaly cases, 61 stillbirth cases, and 48 neonatal death cases were compared with that of 998 normal controls. After controlling for confounding variables, we found that the Vietnam veterans’ relative risk of fathering an infant with one or more major malformations was 1.7 (95% CI = 0.8, 3.5) compared to non-Vietnam veterans. The increased risk was present in several organ systems and did not seem to be related to a particular type of defect. No associations or highly unstable associations were found between paternal military service in Vietnam and the occurrence of
congenital anomalies overall, minor malformations, normal variants, stillbirths, and neonatal deaths.


Total serum testosterone and gonadotropins in workers exposed to dioxin.


**Abstract:** Human reproductive endocrine data may be an important source of epidemiologic information in regard to the toxic potential of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin). The association of serum dioxin with total serum testosterone, luteinizing hormone, and follicle-stimulating hormone was examined in 248 chemical production workers from New Jersey and Missouri plants and 231 nonexposed neighborhood referents who participated in a medical evaluation in 1987.


Vietnam veterans’ risks for fathering babies with birth defects.

**Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, McClearn AB, Adams MJ Jr.**

**Abstract:** Vietnam veterans’ risks for fathering babies with major structural birth defects were assessed using a case-control study. Information regarding military service in Vietnam was obtained from interviews with mothers and fathers of babies in case and control groups and from review of military records. Vietnam veterans, in general, did not have an increased risk of fathering babies with defects (all types combined; relative risk estimate, 0.97).
Vietnam veterans who had greater estimated opportunities for Agent Orange exposure did not seem to be at greater risk for fathering babies with all types of defects combined. However, for a few specific types of defects the estimated risks were higher for subgroups of Vietnam veterans that may have had a greater likelihood of exposure to Agent Orange. These seemingly higher risks could be chance events, the result of some experience in the Vietnam service of the father, or the result of some other unidentified risk factor.


Reproductive behaviour and consistent patterns of abnormality in offspring of Vietnam veterans.

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In view of the persistent claim of Australian Vietnam veterans that their health and that of their children were adversely affected, aspects of reproductive behaviour and the distribution of disease and disability in family units were investigated in a sample of Tasmanian veterans and another group chosen for comparison of selected characteristics. One third of veterans reported serious health problems and their reproductive behaviour differed with more marital breakdowns, increased use of reproductive alternatives, and more complications of pregnancy. Patterns of malformation and disease among veterans’ children involved predominantly the central nervous, skeletal, and cardiovascular systems. A similar pattern was detected on review of the three other major investigations on veterans’ offspring in the USA and Australia. Although plausible mechanisms remain unknown, the evidence
from all available studies supports a causal contribution to defects in veterans’ children from a paternally mediated genetic effect.


Evaluation of chromosomal damage in males exposed to agent orange and their families.

Kaye CI, Rao S, Simpson SJ, Rosenthal FS, Cohen MM.

Agent Orange (AO), a phenoxyherbicide, and dioxin, an impurity found in AO, are considered clastogens, mutagens, and teratogens in plants and animals. AO has come under suspicion in humans following claims that it causes chromosome damage and birth defects in offspring of exposed individuals. No well-designed epidemiological studies are available to support this conclusion. Of ten exposed individuals studied for chromosome breaks and sister chromatid exchange frequencies, eight were ascertained because they had children with congenital defects. No consistent pattern of anomalies was observed. Five children had neurologic deficit, one child had a central nervous system anomaly, and one child was affected with glaucoma. Although all individuals studied had normal karyotypes, a statistically significant increase in chromosome breakage was observed in exposed males compared to their unexposed wives and children; sister chromatid exchange frequency was not increased.


Parental occupation and childhood astrocytoma: results of a case-control study.

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Parental occupations were investigated as possible risk factors for astrocytoma, the most frequently occurring brain tumor in children. A case-control study of 163 pairs was performed. Cases under 15 years of age at diagnosis in 1980-1986 were identified through the tumor registries of eight hospitals in Pennsylvania, New Jersey, and Delaware. Controls were selected by random-digit dialing and were matched to cases on age, race, and telephone area code. Occupations before the child’s conception, during the pregnancy, and after the child’s birth were studied separately. We did not observe any strong associations. Significantly more fathers of cases were electrical or electronic repairmen, a subgroup of an occupational category previously associated with increased risk. An excess of case mothers employed as nurses was observed, which was significant for mothers of children diagnosed before 5 years of age. Elevated although not significant odds ratios were observed for some white collar and professional occupations in case parents; for paternal exposure to paint and paternal occupation in the paper and pulp mill industry, both in the period after the child’s birth; and for maternal occupation as a hairdresser. The lack of strong associations may have resulted from low statistical power for some job groupings. Our study, unlike previous studies, focused on a single type of brain tumor: childhood astrocytoma. Thus our results suggest that some parental occupations associated with childhood brain tumors in previous studies may not be risk factors for childhood astrocytoma.


Cytogenetic effects from exposure to mixed pesticides and the influence from genetic susceptibility.

Au WW, Sierra-Torres CH, Cajas-Salazar N, Shipp BK, Legator MS.
Exposure to pesticides remains a major environmental health problem. Health risk from such exposure needs to be more precisely understood. We conducted three different cytogenetic assays to elucidate the biological effects of exposure to mixed pesticides in 20 Costa Rica farmers (all nonsmokers) compared with 20 matched controls. The farmers were also exposed to dibromochloropropane during the early employment years, and most of them experienced sterility/fertility problems. Our data show that the farmers had consistently higher frequencies of chromosome aberrations, as determined by the standard chromosome aberration assay, and significantly abnormal DNA repair responses (p < 0.05), as determined by the challenge assay, but no statistically significant differences in the tandem-probe fluorescence in situ hybridization (FISH) assay (p > 0.05). Genotype analysis indicates that farmers with certain “unfavorable” versions of polymorphic metabolizing genes (cytochrome P4502E1, the glutathione S-transferases mu and theta, and the paraoxonase genes) had significantly more biological effects, as determined by all three cytogenetic assays, than both the farmers with the “favorable” alleles and the matched controls. A unique observation is that, in individuals who had inherited any of the mentioned “unfavorable” alleles, farmers were consistently underrepresented. In conclusion, the Costa Rican farmers were exposed to genotoxic agents, most likely pesticides, which expressed the induction of biological and adverse health effects. The farmers who had inherited “unfavorable” metabolizing alleles were more susceptible to genotoxic effects than those with “favorable” alleles. Our genotype data suggest that the well-recognized “healthy worker effect” may be influenced by unrecognized occupational selection pressure against genetically susceptible individuals.

Study of reproductive function in persons occupationally exposed to 2,4-dichlorophenoxyacetic acid (2,4-D).

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We studied the reproductive function of 32 male farm sprayers who were exposed to 2,4-D. Sperm analysis was made after 4 days of sexual inactivity. Parameters analyzed were volume, sperm count, mobility and morphology. Exposure level was estimated by measuring the concentration of 2,4-D in the urine. Significant levels of asthenospermia, necrospermia and teratospermia were found in exposed workers compared with unexposed controls. Over time, asthenospermia and necrospermia diminished but the abnormal spermatozoa (teratospermia) continued.


Birth defects among offspring of firemen.

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The authors conducted an exploratory case-control study of paternal employment as a fire fighter and the risk of birth defects among offspring. Among the 20 birth defect groups studied, an association was found for paternal employment as a fire fighter (relative to all other occupations) and increased risks were observed for ventricular septal defects (odds ratio (OR) = 2.70, 95% confidence interval (CI) 1.02-7.18) and atrial septal defects (OR = 5.91, 95% CI 1.60-21.83).
among offspring. When compared with policemen, firemen had increased risks of having a child with a ventricular septal defect (OR = 4.68, 95% CI 1.66-13.17) and atrial septal defect (OR = 3.76, 95% CI 1.40-10.07).


Congenital glaucoma and retinal dysplasia.

Preslan MW, Beauchamp GR, Zakov ZN.

The differential diagnosis of leukocoria (pseudogioma) in the neonate includes multiple conditions, including malformations with retinal dysplasia as a component. Typically bilateral, retinal dysplasia is characteristically seen in microphthalmic eyes. Certain chromosomal defects have been described. The case reported herein presented in the first month of life with an enlarged eye, elevated intraocular pressure, prominent iris vasculature, and leukocoria. Family history was positive in one respect: this is the second child of a Viet Nam veteran exposed to Agent Orange. The first child, from a different mother, also had birth defects. Other than his left eye, the child is completely normal. Ultrasonography showed posterior vitreous opacities of indeterminate configuration. CT scan suggested a posterior intraocular mass. Histologically, the principal features were an anomalous, largely unformed corneoscleral angle, intraocular hemorrhage, and retinal dysplasia. Light microscopic studies were performed. The corneoscleral angle revealed an anteriorly inserted iris with an absence of trabecular meshwork and Schlemm’s canal. This case is considered unique on the basis of the association of retinal dysplasia with congenital glaucoma and larger-than-normal eye. The significance of reported paternal exposure to Agent Orange in this instance is unknown.

Spermatozoa were the first cell type in which the cellular generation of reactive oxygen was demonstrated. This activity has now been confirmed in spermatozoa from all mammalian species examined including the rat, mouse, rabbit, horse, bull and human being. Under physiological circumstances, cellular redox activity is thought to drive the cAMP-mediated, tyrosine phosphorylation events associated with sperm capacitation. In addition to this biological role, human spermatozoa also appear to suffer from oxidative stress, with impacts on the normality of their function and the integrity of their nuclear and mitochondrial DNA. Recent studies have helped to clarify the molecular basis for the intense redox activity observed in defective human spermatozoa, the nature of the subcellular structures responsible for this activity and possible mechanisms by which oxidative stress impacts on these cells. Given the importance of oxidative damage in the male germ line to the origins of male infertility, early pregnancy loss and childhood disease, this area of sperm biochemistry deserves attention from all those interested in improved methods for the diagnosis, management and prevention of male-mediated reproductive failure.


Lead: male-mediated effects on reproduction and development in the rat.
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The present study was designed to determine the effect of relatively low levels of lead acetate (25 and 250 ppm) exposure on fertility and offspring viability in male Sprague-Dawley rats. Protein synthesis in 2-cell embryos was monitored by [35S] methionine labeling and two-dimensional SDS gel electrophoresis. Fertility was reduced in males with blood lead levels in the range 27-60 microg/dL. Lead was found to affect initial genomic expression in embryos fathered by male rats with blood lead levels as low as 15-23 microg/dL. Dose-dependent increases were seen in an unidentified set of proteins with a relative molecular weight of approximately 70 kDa (Mr). These results indicate that male-mediated effects of lead may be observed in the 2-cell embryo. The alteration observed in embryonic gene expression with paternal lead exposure may be useful for studying the role of the paternal contribution to the activation of the embryonic genome and protein synthesis in the early embryo. Copyright 1999 Academic Press.


Health and reproductive outcomes among American Legionnaires in relation to combat and herbicide exposure in Vietnam.

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**Abstract:** History of diagnosed illnesses, medical symptoms, and reproductive outcomes and their relation to combat intensity and herbicide exposure were studied, via a mailed questionnaire, among 6810 American Legionnaires who served during the Vietnam War (42% in Southeast Asia, 58% elsewhere). The percentage of spouses’ pregnancies which resulted in miscarriages was significantly higher for Vietnam veterans than controls (7.6% vs 5.5%, P less than 0.001). Logistic regression analysis showed that Agent Orange exposure and maternal smoking were both independently and significantly associated with miscarriage rates in a dose-related manner.


Health effects of phenoxy herbicides. A review.

**Sterling TD, Arundel AV.**

A review of epidemiological studies on the health effects of exposure to phenoxy herbicides suggests that exposure may be associated with an increased incidence of cancer and unfavorable outcomes of pregnancy. Studies on cancer have found increased risks of 5.3, 6.8 and 3.96 for soft-tissue sarcoma, 7.7 and 6.0 for stomach cancer, 2.05 for lung cancer, 4.8 for lymphoma, 2.3 for all cancers combined, and 5.2 for liver cancer after exposure to 2,4,5-T or dioxin contaminants. Several studies have suggested a possible increase in birth defects after paternal exposure. An increased risk of hydatidiform mole is suggested by Vietnamese studies on the effects of maternal exposure.

Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand.


Armstrong Laboratory, Brooks Air Force Base, San Antonio, TX.

Comment in:


We studied whether paternal exposure to Agent Orange and its dioxin contaminant (2,3,7,8-tetrachlorodibenzo-p-dioxin) during the Vietnam War is related to adverse reproductive outcomes after service in Southeast Asia. The index cohort comprises conceptions and children of veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam from 1962 to 1971. The comparison cohort comprises conceptions and children of Air Force veterans who served in Southeast Asia during the same period but who were not involved with spraying herbicides. We found no meaningful elevation in risk for spontaneous abortion or stillbirth. In analyses of birth defects, we found elevations in risk in some organ system categories, which, after review of the clinical descriptions, were found to be not biologically meaningful. There was an increase in nervous system defects in Ranch Hand children with increased paternal dioxin, but it was based on sparse data. We found no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin. These data provide little or no support for the theory that paternal exposure to Agent Orange and its dioxin contaminant is associated with adverse reproductive outcomes.

Paternal occupation and risk of birth defects in offspring.

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Several epidemiologic studies indicate that some paternal occupations are associated with an increased risk of birth defects in offspring. We evaluated this relation using data from a population-based case-control study. Cases are infants with a major birth defect registered with the Metropolitan Atlanta Congenital Defects Program between 1968 and 1980. We selected controls from livebirths in the Atlanta area using frequency matching for race, year, and hospital of birth. Case and control parents were interviewed to solicit information on several factors, including occupation. We classified paternal occupation according to the job held during the time from 6 months before until 1 month after the estimated date of conception. We compared fathers in one occupational category with fathers in all other categories combined. We identified a number of associations including: firemen with cleft lip [odds ratio (OR) = 13.3; 95% confidence interval (CI) = 4.0-44.4]; painters with atrial septal defect (OR = 2.7; 95% CI = 1.0-7.4); and farmers with cleft lip and palate (OR = 3.3; 95% CI = 0.9-11.9). This study, however, did not corroborate several associations found in previous studies, such as painters and neural tube defects. We identified several additional occupations as potential risk factors for some defects, including printers, electronic equipment operators, and vehicle manufacturers.


Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment.

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In this study of cancer in offspring we demonstrate that factors linked to horticulture and use of pesticides are associated with cancer at an early age, whereas factors in animal husbandry, in particular poultry farming, are associated with cancers in later childhood and young adulthood. Incident cancer was investigated in offspring born in 1952-1991 to parents identified as farm holders in agricultural censuses in Norway in 1969-1989. In the follow-up of 323,292 offspring for 5.7 million person-years, 1,275 incident cancers were identified in the Cancer Registry for 1965-1991. The standardized incidence for all cancers was equal to the total rural population of Norway, but cohort subjects had an excess incidence of nervous-system tumours and testicular cancers in certain regions and strata of time that could imply that specific risk factors were of importance. Classification of exposure indicators was based on information given at the agricultural censuses. Risk factors were found for brain tumours, in particular non-astrocytic neuroepithelial tumours: for all ages, pig farming tripled the risk [rate ratio (RR), 3.11; 95% confidence interval (CI), 1.89-5.13]; indicators of pesticide use had an independent effect of the same magnitude in a dose-response fashion, strongest in children aged 0 to 14 years (RR, 3.37; 95% CI, 1.63-6.94). Horticulture and pesticide indicators were associated with all cancers at ages 0 to 4 years, Wilms’ tumour, non-Hodgkin’s lymphoma, eye cancer and neuroblastoma. Chicken farming was associated with some common cancers of adolescence, and was strongest for osteosarcoma and mixed cellular type of Hodgkin’s disease. The main problem in this large cohort study is the crude exposure indicators available; the resulting misclassification is likely to bias any true association towards unity.

Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry.

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OBJECTIVES: The purpose of the study was to determine whether paternal occupational exposure to dioxin-contaminated chlorophenols is associated with an increased risk of congenital anomalies or other adverse reproductive outcomes in offspring.

METHODS: As a result of a multistep linkage, 19675 births between 1952 and 1988 were identified as children of a cohort of 9512 fathers who had worked at least one year in British Columbia sawmills where chlorophenate wood preservatives had been used. A nested case-referent analysis was applied, using conditional logistic regression, with five referents matched per case according to year of birth and gender. Chlorophenate exposure was based on expert raters’ estimations of hours of exposure applied to specific time windows prior to birth. RESULTS: The offspring of male sawmill workers were at increased risk for developing congenital anomalies of the eye, particularly congenital cataracts; elevated risks for developing anencephaly or spina bifida and congenital anomalies of genital organs were shown according to specific windows of exposure. No associations were found for low birthweight, prematurity, stillbirths, or neonatal deaths. CONCLUSIONS: The study adds further support to the hypothesis of male-mediated developmental toxicity. Paternal exposure to chlorophenates was associated with the development of certain congenital anomalies in offspring.

32) The male reproductive system and its susceptibility to endocrine disrupting chemicals

1. Pflieger-Bruss, H.-C.Schuppe and W.-B.Schill
Summary. In the past years, there has been increased interest in assessing the relationship between impaired male fertility and environmental factors. Human male fertility is a complex process and therefore a great variety of sites may be affected by exogenous noxae. Lifestyle factors as well as various environmental and occupational agents may impair male fertility. Many studies have been published reporting on reproductive dysfunctions in male animals and humans. Especially environmental pollutants with endocrine activity are discussed as a possible cause of this detrimental development. Evidence from animal experiments show that substances with oestrogenic and antiandrogenic properties may cause hypospadia, cryptorchidism, reduction of sperm density and an increase of testicular tumours. Many adverse effects on animal male fertility have been documented for phthalates and some chlorinated hydrocarbons such as polychlorinated biphenyls and polychlorinated dibenzo-p-dioxins. For other chemicals such as bisphenol A and nonylphenols animal data are conflicting. Environmental pollutants may mediate their effects by receptor binding, modulation of hormone-regulated mechanisms or direct toxic effects. Data on environmental chemicals and human male fertility are scarce, and risk assessment is mostly based on the results of animal studies. However, there are indications that exposure to endocrine active chemicals during early development...
may alter hormone responsiveness in adulthood. Furthermore, some of the chemicals are found in fluids that are associated with human reproduction, such as follicular fluid, seminal fluid and cervical mucus. Recent studies suggest a correlation between pesticide exposure and standard semen parameters as well as in vitro fertilization rates.

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Association of male infertility with Pro185Ala polymorphism in the aryl hydrocarbon receptor repressor gene: Implication for the susceptibility to dioxins by Masanori Watanabe, Kou Sueoka, Isoji Sasagawa, Akira Nakabayashi, Yasunori Yoshimura, Tsutomu Ogata

Abstract: The Pro185Ala polymorphism in AHRR may constitute a susceptibility locus for dioxin-related male infertility. It appears that the negative feedback effect of AHRR on dioxin-related signaling is weaker for the proline allele than for the alanine allele, and that the hypomorphic function of the proline allele exerts a recessive adverse effect on male fertility.


Exposure to persistent organochlorine pollutants associates with human sperm Y:X chromosome ratio

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Abstract: This is the first study to indicate that exposure to POPs may increase the proportion of ejaculated Y-bearing spermatozoa. These data add to the growing body of evidence that exposure to POPs may alter the offspring sex ratio.


Environmental toxicant-induced germ cell apoptosis in the human fetal testis

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Abstract: Disorders of the male reproductive system are increasing in prevalence. The term testicular dysgenesis syndrome emphasizes the importance of developmental influences on the aetiology of conditions including cryptorchidism, testicular germ cell cancer and reduced spermatogenesis. Men whose mothers smoked during pregnancy have lower sperm production. Cigarette smoke contains agents acting on the aryl hydrocarbon receptor (AHR). We have investigated the presence of AHR in the developing human testis and the effects of functional activation. Germ cells in the developing human testis are a target for regulation by AHR ligands. Activation of AHR by environmental toxicants and AHR-induced apoptotic pathways may be the mechanism of action underlying the epidemiological findings of reduced spermatogenesis in men exposed to cigarette smoke before birth, and may also be of importance in other conditions comprising the testicular dysgenesis syndrome.